

# SPECIFICATION

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## ***TREATMENT OF MENORRHAGIA, HYPERMENORRHEA, DYSMENORRHEA AND MENSTRUAL MIGRAINES BY THE ADMINISTRATION OF AN ANTIBACTERIAL MILK PRODUCT***

### **Background of Invention**

- [0001] Many women suffer from menorrhagia, hypermenorrhea, dysmenorrhea, menstrual migraines and combinations thereof.
- [0002] Menorrhagia is defined as excessive menstrual bleeding in the absence of organic pathology. Hypermenorrhea is defined as excessive duration of menstruation in the absence of organic pathology. Menorrhagia and hypermenorrhea have no known etiology. It has, however, been postulated that menorrhagia and hypermenorrhea are the result of an inappropriate exposure of the endometrium to hormones. Menorrhagia is an exceedingly common problem, typically comprising approximately one in five outpatient referrals to gynecological departments. Women suffering severe menorrhagia are at risk for chronic anemia. Hypermenorrhea is also an exceedingly common problem.
- [0003] Dysmenorrhea is a term used to describe painful menstruation. The pain may range from minor cramping to intense pain accompanied by diarrhea, nausea and vomiting, with sensations of pelvic heaviness and breast fullness.
- [0004] Menstrual migraines is a term used to describe migraines which accompany menstruation.

[0005] Mankind has sought ways to treat menorrhagia, hypermenorrhea, dysmenorrhea and menstrual migraines, including efforts ranging from the consumption of specific foods to drug therapy such as treatment with oral contraceptives or progestin. While certain of these techniques have demonstrated limited success in decreasing the severity of menorrhagia, hypermenorrhea, dysmenorrhea and/or menstrual migraines, the search continues for drug-free alternatives.

## Summary of Invention

[0006] I have discovered that menorrhagia, hypermenorrhea, dysmenorrhea and menstrual migraines can be treated by administering a therapeutic amount of an antibacterial milk product.

## Detailed Description

[0007] *Definitions*

[0008] As utilized herein, the phrase *antibacterial milk product* means antibacterial milk obtained in accordance with the process set forth in United States Reissue Patent No. Re. 33,565, the disclosure of which is hereby incorporated by reference, and any active fraction of such antibacterial milk, including specifically, but not exclusively, skimmed antibacterial milk, antibacterial powdered whole milk, antibacterial skimmed powdered milk, concentrated antibacterial powdered whole milk, and concentrated antibacterial skimmed powdered milk.

[0009] As utilized herein, the phrase *active fraction*, when used in connection with antibacterial milk, means a preparation or composition extracted from the antibacterial milk which retains the desired therapeutic property of the unextracted antibacterial milk due to the presence of derivatized and processed forms of the allergens used to immunize the animal providing the antibacterial milk.

[0010] As utilized herein, the phrase *antibacterial powdered milk* means antibacterial milk obtained in accordance with the process set forth in United States Reissue Patent No. Re. 33,565, which has optionally been skimmed to remove fat and has been dried to form a powdered milk.

[0011] As utilized herein, the phrase *antibacterial powdered skimmed milk* means

antibacterial milk obtained in accordance with the process set forth in United States Reissue Patent No. Re. 33,565, which has been skimmed to remove fat and has been dried to form a powdered milk.

- [0012] As utilized herein, the phrase *concentrated antibacterial powdered milk* means antibacterial powdered milk which has optionally been skimmed to remove fat, separated to remove lactose and salt, and dried to form a concentrated powdered milk.
- [0013] As utilized herein, the phrase *concentrated antibacterial powdered skimmed milk* means antibacterial powdered milk which has been skimmed to remove fat, separated to remove lactose and salt, and dried to form a concentrated powdered milk.
- [0014] *Antibacterial Milk Product*
- [0015] Antibacterial milk, from which various antibacterial milk products can be extracted, can be produced in accordance with the process set forth in United States Reissue Patent No. Re. 33,565, the disclosure of which is hereby incorporated by reference. A synopsis of the process, as described in United States Reissue Patent No. Re. 33,565, is provided below.
- [0016] *Preparation of the Vaccine*
- [0017] The bacteria strains listed in Table One, obtained from the American Type Culture Collection, are individually grown on a blood agar plate to test the viability of the culture and determine if growth pattern is typical or atypical of the bacteria in question. A single colony from each of the test cultures is taken for histological examination to further ensure authenticity and purity of the culture. A single colony of each culture is used to inoculate 500 ml of standard culture broth as recommended by the American Type Culture Collection.

[0018] TABLE ONE

[t2]

<i>Bacterial Antigens</i>	
ORGANISM	*ATCC NO.

<i>Staphylococcus aureus</i>	11631
<i>Staphylococcus epidermidis</i>	155
<i>Streptococcus pyogenes</i> A. Type 1	8671
<i>Streptococcus pyogenes</i> A. Type 3	10389
<i>Streptococcus pyogenes</i> A. Type 5	12347
<i>Streptococcus pyogenes</i> A. Type 8	12349
<i>Streptococcus pyogenes</i> A. Type 12	11434
<i>Streptococcus pyogenes</i> A. Type 14	12972
<i>Streptococcus pyogenes</i> A. Type 18	12357
<i>Streptococcus pyogenes</i> A. Type 22	10403
<i>Aerobacter aerogenes</i>	884
<i>Escherichia coli</i>	26
<i>Salmonella enteritidis</i>	13076
<i>Pseudomonas aeruginosa</i>	7700
<i>Klebsiella pneumoniae</i>	9590
<i>Salmonella typhimurium</i>	13311
<i>Haemophilus influenzae</i>	9333
<i>Streptococcus mitis</i>	
<i>Proteus vulgaris</i>	13315
<i>Shigella dysenteriae</i>	11835
<i>Diplococcus pneumoniae</i>	
<i>Propionibacter acnes</i>	
<i>Streptococcus sanguis</i>	
<i>Streptococcus salivarius</i>	
<i>Streptococcus mutans</i>	
<i>Streptococcus agalactiae</i>	

- [0019] All organisms are incubated as static cultures with the exception of *Escherichia coli*, *Salmonella enteritidis*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*, which are incubated in a shaker to provide agitation. Identification of bacterial strains

and the American Type Culture Collection catalog numbers are shown in Table One. Each culture is cultivated for 48 hours at 37 ° C. Following incubation, the cultures are killed by heating at 60 ° C for two hours. Samples of the killed bacteria are used to inoculate fresh broth, which is then incubated for 24 hours at 37 ° C to confirm that the killing process was complete. Only cultures proven sterile by this procedure are used for further processing. Sterile cultures are washed five times in distilled water and the cells recovered by centrifugation. The bacterial cells are frozen by immersion in liquid nitrogen and freeze-dried by lyophilization. The lyophilized cells are stored in sterile vials until used for production of the polyvalent vaccine.

[0020] A polyvalent vaccine is prepared by weighing out one gram quantities of each of the bacterial strains. The dry cells were mixed together and this mixture is suspended in sterile physiological saline (20 grams of bacteria per 500 ml saline).

[0021] A sample of the concentrated solution is diluted in serial fashion with saline to determine the dilution, which gives a concentration of  $4 \times 10^8$  CL per cc. The stock concentrated polyvalent vaccine is dispersed into multiple containers and stored frozen. A sufficient amount of concentrated antigen is included in each individual container to immunize 50 cows. The final dilution of concentrate is made just prior to immunization. The preferred procedure is to remove a sufficient number of vials to immunize the number of cows to be treated. For example, the vials are removed 24 hours prior to the planned time of immunization; a sample of the concentrate is then diluted in a sterile container to a final concentration of  $4 \times 10^8$  cells per ml. The maximum response in cows is obtained by injecting  $20 \times 10^8$  bacterial cells or 5 cc of the sterile preparation, which is  $4 \times 10^8$  cells per ml according to the method on immunization described below.

[0022] *Preferred Process for Immunization of Cows*

[0023] Cows are injected with 5 cc of polyvalent antigen containing  $20 \times 10^8$  bacterial cells. The injection is made intramuscularly in the gluteus maximus muscle of the hind leg. This procedure is repeated at one-week intervals for four consecutive weeks beginning 2–3 weeks prior to the predicted day of parturition. Following the primary immunization, booster injections using the same concentration of the antigen are given every 14 days. This method of immunization gives the maximum antibody titer.

[0024] *Collection, Handling and Processing of Milk*

[0025] The milk is collected from immunized cows in a modern dairy parlor. A fully automated milking system collects and stores the milk under complete sanitary conditions. The milking system consists of automated machines connected directly to refrigerated storage tanks by a closed system of pipes. The complete system is cleaned and sterilized following each milking to ensure maximum sanitary conditions. It is important to take careful steps to prevent the growth of bacteria in the antibacterial milk during processing, since such bacteria can lower the concentration of proteins in the milk.

[0026] Milk is transported daily from the refrigerated holding tanks to a dairy processing plant by milk transport trucks. At the dairy plant, a high temperature short-time system is used to pasteurize the antibacterial milk. Specialized dairy machinery provides the flash heating of a continuous flow of milk to 155 ° F for a period of not more than 15 seconds. Temperature and time is critical since proteins are susceptible to degradation by heat. Milk proteins are destroyed at temperature above 165 ° F if held for periods longer than one minute.

[0027] Following pasteurization, the whole milk is immediately cooled, fat is removed by centrifugation to produce skimmed antibacterial milk, and the skimmed antibacterial milk is powdered by a spray-drying process. The spray-drying process consists of a large drying chamber into which hot air (350 ° F) is blown at high velocity. The skimmed milk is atomized into the chamber where the finely divided milk particle are instantly dried as they fall to the bottom of the tank. The dried milk is removed automatically by means of mechanical devices and the milk powder is packaged under sanitary conditions. Prior to atomizing, the skimmed milk is condensed by boiling in a chamber under vacuum at a temperature of 100 to 110 ° F. At each step, it is critical to keep bacteria from contaminating the milk since this reduces the concentration of milk proteins.

[0028] *Concentration of Milk*

[0029] A concentrated form of the antibacterial milk in which about 95% of the lactose and salt is removed can be obtained by ultrafiltration of the pasteurized skimmed

antibacterial milk through a membrane or molecular sieve that retards molecules with a molecular weight of greater than 100,000 as set forth in United States Patent No. 5,106,618, the disclosure of which is hereby incorporated by reference. Since immunoglobulins have molecular weights well in excess of 100,000 while lactose has a molecular weight well below 100,000, lactose is effectively separated from the immunoglobulin milk proteins. This permits a 10 to 100 fold concentration, typically about a 30 fold concentration, of the milk proteins.

- [0030] Such concentration of the antibacterial milk reduces the mass to such an extent that capsules containing an effective amount of the milk proteins can be formulated from concentrated antibacterial powdered skimmed milk.
- [0031] Commercial Availability of Antibacterial Milk Products Concentrated antibacterial powdered skimmed milk, manufactured in accordance with the process described above and useful in the treatment of menorrhagia, hypermenorrhea, dysmenorrhea and menstrual migraines in accordance with the treatment method disclosed herein, is commercially available from AdvantRx Corporation of Chanhassen, Minnesota and Stolle Milk Biologics, Inc. of Cincinnati, Ohio under the mark MicroLactin™ .
- [0032] *Administration*
- [0033] *Administration Route*
- [0034] The antibacterial milk product can be administered by virtually any of the commonly accepted practices for the administration of pharmaceutical preparations including specifically, but not exclusively, mucosal administration, oral consumption, ocular administration, subcutaneous injection, transdermal administration, etc.
- [0035] Mucosal administration of the antibacterial milk product includes such routes as buccal, endotracheal, nasal, pharyngeal, rectal, sublingual, vaginal, etc. For administration through the buccal/sublingual/pharyngeal/endotracheal mucosa, the antibacterial milk product may be formulated as an emulsion, gum, lozenge, spray, tablet or an inclusion complex such as cyclodextrin inclusion complexes. Nasal administration is conveniently conducted through the use of a sniffing power or nasal spray. For rectal and vaginal administration the antibacterial milk product may be formulated as a cream, douch, enema or suppository.

- [0036] Oral consumption of the antibacterial milk product may be effected by incorporating the antibacterial milk product into a food or drink, or formulating the antibacterial milk product into a chewable or swallowable tablet.
- [0037] Ocular administration may be effected by incorporating the antibacterial milk product into a solution or suspension adapted for ocular application such as drops or sprays.
- [0038] Subcutaneous administration involves incorporating the antibacterial milk product into a pharmaceutically acceptable and injectable carrier.
- [0039] For transdermal administration, the antibacterial milk product may be conveniently incorporated into a lipophilic carrier and formulated as a topical creme or adhesive patch.
- [0040] Oral administration is preferred due to ease of administration and cost.
- [0041] *Dose Rate*
- [0042] The range of dosages and dose rates effective for achieving the desired biological properties and characteristics may be determined in accordance with standard industry practices. These ranges can be expected to differ depending upon whether the desired response is the prophylactic, modulatory, ameliorative or curative in nature.
- [0043] Generally, daily oral administration of about 45 to about 90 grams of antibacterial powdered skimmed milk, or about 1 to about 4 grams of concentrated antibacterial powdered skimmed milk should be effective. Alternatively, the antibacterial low-fat milk product may be administered only during menstruation.
- [0044] *Experimental*
- [0045] *Experiment 1*
- [0046] One female subject, age 41, afflicted with moderate menorrhagia, hypermenorrhea and dysmenorrhea and severe menstrual migraines orally consumed two 500 mg capsules of MicroLactin™ twice daily (hereinafter MicroLactin™ Treatment Regimen) for four (4) months. She reported a significant decrease in both

the duration and amount of menstruation, a lessening of menstrual cramping and a complete absence of menstrual migraines while on the MicroLactin™ Treatment Regimen. She then discontinued the MicroLactin™ Treatment Regimen upon the conclusion of menstruation in the fourth month and reported a return to pretreatment conditions in the duration and amount of menstruation, severity of menstrual cramping and occurrence of a debilitating menstrual migraine during the untreated menstruation. She restarted the MicroLactin Treatment Regimen shortly after completion of her untreated menstruation and again reported a significant decrease in both the duration and amount of menstruation, a lessening of menstrual cramping and a complete absence of menstrual migraines during subsequent menstruations.